REMARKS/ARGUMENTS

In response to the Office Action mailed March 18, 2010, Applicant amends his application and requests reconsideration. Claims 1-25 were originally pending in this application. Claims 1-10, 13, 15-16, and 18-26 are cancelled, and claims 11-12, 14, 17 and 27-28, are pending and undergoing examination.

Claim Amendments

Claim 11 was amended to further clarify and refine that which Applicant considers to be the claimed invention. Applicant has amended the first transitional phrase of claim 11 to recite "consisting of."

Solely for the purpose of advancing prosecution of the instant application, Applicant has cancelled claim 13 directed to a transplant comprising human corneal endothelial cells. Applicant reserves the right to reinstate this claim in a continuation or divisional application.

Discussion of the Obviousness Rejection

The Examiner has maintained the rejection of claims 11-17 under 35 U.S.C. §103(a), as unpatentable, over Parenteau et al., in view of USP 6,645,715 to Griffith et al., and USP 6,689,165 to Jacob et al. for the reasons made previously of record. Applicant traverses this rejection.

In view of Applicant's claim amendments, Applicant submits that both Parenteau et al. and Griffith et al. are directed to artificial corneal models or artificial corneas containing various cell types. Applicant's claimed invention does not include corneal cells or any other cell type in the claimed construct. Moreover, Applicant's amended claims do not include the use of heparin, or heparin binding growth factor, as mentioned in the Examiner's remarks.

On page 5 of the Office Action, the Examiner indicates that Applicant's second transitional phrase of claim 11 b) "consisting essentially of," is being interpreted as "comprising," because it is unclear to the Examiner what the basic and novel characteristics are of Applicant's claim, citing *PPG Industries v. Guardian*

Industries, 156 F.3d 1351, 48 USPQ2d 1351 (Fed Cir. 1998). Applicant submits that it is clear to one of ordinary skill in the art as to what the basic and novel characteristics of Applicant's claim are. Briefly, Applicant's novel characteristics include an artificial corneal transplant support, which is capable of sustaining the growth of human corneal endothelial cells on its concave side, and is also capable of being transplanted *in vivo* into a damaged cornea of a patient. Within that context, when reading claim 11, paragraph b), one of ordinary skill in the art would understand that the compounds recited in b) are growth and attachment factors which assist in the growth and attachment of the corneal endothelial cells on the transplant support. Thus, the claim would be understood not to encompass other growth and attachment factors other than those identified in the claim.

The Examiner, on pages 5 and 6 of the Office Action, disagrees with Applicant regarding the dimensions and teachings of the corneal model taught by Parenteau et al. Applicant's point with regard to this issue, is that what is taught in Parenteau is not suitable for use as a corneal endothelial transport support, as claimed by Applicant, and it is not enabled for this purpose. It is the Examiner's contention that because Parenteau et al. teach that the model has all of the cell types and layers, and that Parenteau et al. state (at col. 10, lines 11-24) that it can be used for ocular wound closure and repair, that the model taught in Parenteau et al. must have the equivalent thickness or dimensions of the average corneal thickness or half-thickness as claimed by Applicant. The Examiner's assumption does not comport with the dimensions of the corneal model disclosed in Parenteau et al.

To being with, the dimensions of the corneal model taught in Parenteau et al. are significantly larger that an actual human cornea. The corneal model of Parenteau et al. is disclosed in detail at columns 5 and 6, and Figs. 11A to 11D. Parenteau et al. seed human corneal endothelial cells (HCEC) onto a polycarbonate insert which is porous (from 0.2 to 20 μm) and used to allow cells to get nutrients from media underneath the insert. Next, a collagen solution is added to the cell layer (col. 5, lines 40-60), with cell media and allowed to stay for 4 days. It is disclosed that the cell culture insert has an area of 2 cm^2 and 1 ml of collagen is added. Thus, in at least this embodiment, the collagen "biopolymer" layer taught in Parenteau et al. is

approximately 0.5 cm thick. A layer 0.5 cm thick is equivalent to 5000 μm thick, which is 10 times the thickness of the average full-thickness cornea, and which does not include the thickness of the polymer insert. This layer is then allowed to gel. Parenteau et al. teach that the next step is preparing a collagen mixture that contains keratocytes to make a mixture having about 100 keratocytes per μg of collagen. This mixture is then added on top of the HCEC and biopolymer, on the same cell culture insert, and forms a raised area, or mesa, of 2.5 cm^2 (col. 6, lines 42-60, col. 7, lines 8-32). Assuming a circular shape, an area of 2.5 cm^2 translates to a diameter of 1.78 cm or 17.8 mm, which is almost 2X the average width of a human cornea (11 mm). In addition, the difference in surface area of the corneal model is more than 2X larger, with a human cornea having an average area of only 0.95 cm^2. Thus, Parenteau et al. describe a model that is significantly larger that a real cornea, and comports with the teaching of Parenteau et al. that this model is useful for replacement of the rabbit eye test also known as the Draize test (col. 9, 45-65) to examine the cytotoxicity of various compounds on the tissues of the eye, and not useful for an *in vivo* implant. Parenteau et al., therefore, do not teach a corneal model having the thickness of an average cornea or half the average thickness as claimed by Applicant.

Further fault with the suitability of the Parenteau et al. corneal model for use in transplantation, and support is found where Parenteau et al. teach that the actual corneal model is not transparent (col. 10, line 13).

The Examiner's assumption is based on the description of Parenteau et al. at col. 10, lines 1-24. The relevant portion of Parenteau is reproduced below.

> The organotypic culture ***method may*** also be used to form graftable human tissue either as an adjunct to conventional transplantation or as a substitute. The use of cultured corneal endothelial cells has already been shown to be beneficial as a replacement for the often damaged or inadequate endothelium of graft material. (Insler, M.S., Lopez, J.G., "Transplantation of cultured human neonatal corneal endothelium," Curr. Eye Res. 5(12):967-72 (1986).) The use of cultured corneal epithelium has also shown some benefit in promoting wound closure. (Roat, M.I., Thoft, R.A., "Ocular surface epithelial transplantation," Int. Opthalmol. Clin. 28(2):169-174 (1988).) The organotypic corneal construct comprising an endothelium, stroma and epithelium ***could be*** used for ocular wound closure and full-thickness repair of the

> cornea. ***Although not transparent in vitro***, it is ***expected*** that the endothelial cells provided by the construct will regulate fluid transport to the corneal stroma and further stimulate the stromal fibroblasts to continue to organize the matrix and produce the appropriate collagens and glycosaminoglycans necessary for corneal clarity. The in vitro corneal equivalent ***may be*** constructed with more or less extracellular matrix or stroma to facilitate remodeling. Wound closure ***would be*** maintained by the presence of the well-adhered corneal epithelium, thereby limiting hyperproliferation and scarring of the stromal matrix. (col. 9, line 66 to col. 10, line 23, emphasis added)

It is clear to one of ordinary skill in the art, that what this passage in Parenteau et al. teaches is the inventors' idea that the method used to make this *in vitro* corneal equivalent, or model, might be useful *to try* to make an *in vivo* transplant. This is an invitation to try, not an enabling disclosure. The statement by the inventors that the corneal model is not transparent is *prima facie* evidence that the model is unsuitable for Applicant's claimed purpose. The biomedical arts, and especially, the creation of artificial organs and transplants, are too unpredictable for the Examiner, or one of ordinary skill, when reading a passage filled with the conditional terms, "expected," "would be," "may be," which indicate that such an invention would require undue experimentation, to consider the disclosure to be enabled or adequately described to anticipate, or render obvious, the invention claimed by Applicant.

Another example of the unsuitability of the corneal model taught in Parenteau et al.'s for use in *in vivo* transplantation, is in the use of a polymer insert for the endothelial cells. The description and examples all teach the use of a polycarbonate insert onto which the endothelial cells are added, or added on top of a collagen layer that is applied to the insert. That type of polycarbonate biopolymer, while compatible with cells in culture, is rigid, and could not be used for transplantation into the eye. Further deficiency in Parenteau et al. can be found in what is *not* described. Nowhere in Parenteau et al., is there any teaching of how to remove this corneal model from the cell culture system for use in implantation, or whether the insert is included, or is somehow removed. These issues would be critical to making a corneal endothelial support that was suitable for transplantation into the eye, and would also require undue experimentation.

Turning to Griffith et al., the construction of the corneal equivalent in Griffith et al. is similar to Parenteau et al. Cells from the endothelium, stroma and epithelium, are taken from a donor and separated and cultured and immortalized for use as cell lines (Griffith et al., col. 7, lines 5 to 65). The growing cells were then screened for correct morphology.

The next step in Griffith et al. comprises adding trypsinized corneal endothelial cells to a cell culture insert which may be coated with collagen. After growing to 80% confluence, a second layer of collagen and fibronectin is added on top of the endothelial cells, followed by another layer which is a mixture of keratocytes and collagen and chondroitin sulphate. This continues until an epithelial cell layer is eventually added (col. 12, lines 7 to 55).

As with Parenteau et al., nowhere in Griffith et al. is there any teaching of Applicant's acellular corneal transplant support, comprising a biopolymer having the shape and the thickness of a cornea, which has incorporated into it, an attachment reagent consisting essentially of one or more of the following compounds: laminin, fibronectin, RGDS (SEQ ID NO: 1), bFGF conjugated with polycarbophil, and EGF conjugated with polycarbophil, which is suitable for endothelial cell growth and transplantation.

With regards to the teachings of Jacob et al., the Examiner indicated that it did not matter how the growth factors taught in Jacob et al. were attached or combined with the polymer surface. Applicant respectfully disagrees. Jacob et al. teach that proteins and growth factors, when adsorbed or otherwise adhere to synthetic polymers or other surfaces, have interactions with the synthetic or polymer surfaces which can cause minor denaturation or conformational changes in these proteins and growth factors (Jacob et al. at paragraph [0021]).

Jacob et al. then discuss the use of short peptides as molecules that may help cell adhesion. However, Jacob et al. teach that the use of RGD on hydrogels for growing rabbit corneal epithelial cells was not very efficient, and in some cases, actually inhibited cell growth and migration (Jacob et al. at paragraph [0031]). This is

the opposite of what was found by Applicant, and teaches away from one of Applicant's claimed features.

Therefore, one of ordinary skill in the art, would understand that Jacob et al. teach away from Applicant's claimed invention, in which the growth factors, including RGDS, are embedded or incorporated into the biopolymer surface using adsorption or ionic interaction, in the complete opposite way from the hydrogels disclosed in Jacob et al.

With regard to the differences between the cited references and Applicant's invention in view of the amended claims, Applicant submits that none of these references, alone or in combination, teaches an acellular corneal transplant support consisting of a biopolymer in the shape and thickness of an average cornea (or half the average thickness), having a concave and convex side, and having growth and attachment factors consisting essentially of one or more of the following compounds: laminin, fibronectin, RGDS (SEQ ID NO: 1), bFGF conjugated with polycarbophil, and EGF conjugated with polycarbophil, incorporated *within* the biopolymer, that is suitable for transplantation into a damaged cornea, as now claimed by Applicant. It is clear that the Applicant's invention, as now presently claimed, would not have been obvious to one of ordinary skill in the art, at the relevant time, in view of the prior art references. Applicant submits that in view of Applicant's amendments, the combination of teachings of Parenteau et al., in view of Griffith et al. and Jacob et al., do not teach each and every feature of Applicant's claimed invention.

Applicant submits that one of ordinary skill in the art, in an attempt to make an implantable artificial corneal transplant support, would not have looked to Parenteau et al., in view of Griffith et al., and Jacob et al., because both Parenteau et al. and Griffith et al. teach entire corneal models including stroma and epithelial cells, not Applicant's acellular biopolymer support. Moreover, neither of these references teach anything about a corneal transplant support comprising a biopolymer in the shape of a cornea, having a concave and convex side, having the thickness of an average cornea (or half the thickness), and having growth and attachment factors consisting essentially of one or more of the following compounds: laminin, fibronectin, RGDS (SEQ ID NO: 1), bFGF conjugated with polycarbophil, and EGF conjugated with

polycarbophil, incorporated *within* the biopolymer, that is suitable for transplantation into a damaged cornea, as now claimed by Applicant. The methods and reagents used to grow the different cell types in the cited references are not applicable to Applicant's claimed invention, as now amended.

Moreover, Jacob et al. actually teach away from the use of RGD, which is a component of Applicant's claimed attachment reagent, on hydrogels for corneal epithelial cells.

Applicant submits that the combination of Parenteau et al., in view of Griffith et al. and Jacob et al. does not make Applicant's claimed invention *prima facie* obvious, because: 1) the combination of references does not teach each and every element of Applicant's claimed invention, namely, the combination of references does not teach an acellular corneal transplant support consisting of a biopolymer in the shape of a cornea, having a concave and convex side, and having the thickness of an average (or half the average) cornea, and having growth and attachment factors consisting essentially of one or more of the following compounds: laminin, fibronectin, RGDS (SEQ ID NO: 1), bFGF conjugated with polycarbophil, and EGF conjugated with polycarbophil, incorporated *within* the biopolymer, that is suitable for transplantation into a damaged cornea; and 2) the combination of references teaches away from Applicant's invention, because the primary reference of Parenteau et al. and Griffith et al. are directed to constructs containing cells immortalized human corneal endothelial cells (not cells from a patient's cornea), and the secondary reference of Jacob et al. teaches away from Applicant's claimed invention, because it teaches that RGD is not suitable as an attachment reagent on hydrogels for corneal epithelial cells.

Applicant has discussed the teachings of each cited reference, and then has shown that when the *combination of references* is considered, the *combination* of teachings cannot render Applicant's claimed invention, *as a whole*, *prima facie* obvious, because the combination of teachings do not encompass all of Applicant's claimed features, and because the combination of teachings teach away from Applicant's claimed invention. As such, Applicant respectfully requests withdrawal of this rejection.

The Examiner rejected claims 11-14, 17 and 27-28, under 35 U.S.C. §103(a) as obvious over over Parenteau et al., in view of Griffith et al., and Jacob et al. as stated above, and further in view of Thomson et al. (Biomaterials, 1991, 12: 37-40). The Examiner alleges Parenteau et al. teach a full and half-thickness corneal support as recited in claims 11-14, 17, but fails to teach any of the attachment factors claimed by Applicant. Griffith et al. is offered by the Examiner for teaching the attachment factors such as laminin, fibronectin, bFGF and the like. The Examiner offers Jacob et al. for teaching that epithelial cell adhesion is augmented by growth factors on the polymer surface of an artificial corneal construct. The Examiner admits that neither of Parenteau et al., Griffith et al., or Jacob et al. teach the coating of the biopolymer with diamond like carbon as claimed by Applicant. The Examiner offers Thomson for teaching that diamond like carbon (DLC) is inert and suitable for use for growth of cells and biomedical use. The Examiner alleges that it would have been obvious, to one of ordinary skill in the art, at the time Applicant's invention was made, to incorporate the teaching of Thomson et al. to coat the biopolymer in the artificial transplant support with DLC. One of ordinary skill would have been motivated to do so with the expectation of success because it was taught that the coating could improve biocompatibility of the implant in biomedical use and thus improve the artificial corneal transplant in corneal transplantation. Applicant respectfully disagrees.

As stated above, Applicant submits that the combination of Parenteau et al., in view of Griffith et al. and Jacob et al. does not make Applicant's claims 11-12, 14, and 17 *prima facie* obvious, because: 1) the combination of references does not teach each and every element of Applicant's claimed invention, namely, the combination of references does not teach a corneal transplant support consisting of a biopolymer in the shape of a cornea, having a concave and convex side, and having the thickness of an average (or half the average) cornea, and having growth and attachment factors consisting essentially of one or more of the following compounds: laminin, fibronectin, RGDS (SEQ ID NO: 1), bFGF conjugated with polycarbophil, and EGF conjugated with polycarbophil, incorporated *within* the biopolymer, that is suitable for transplantation into a damaged cornea; and 2) the combination of references teaches away from Applicant's invention, because the primary reference of Parenteau et al.

and Griffith et al. are directed to constructs containing cells immortalized human corneal endothelial cells (not cells from a patient's cornea), and the secondary reference of Jacob et al. teaches away from Applicant's claimed invention, because it teaches that RGD is not suitable as an attachment reagent on hydrogels for corneal epithelial cells. This deficiency is not cured by the application of Thomson et al.

Thomson et al. teach that mouse peritoneal macrophages and mouse fibroblasts were grown on tissue culture plates treated with DLC and the biocompatibility assessed both biochemically and morphologically. Thomson et al. found that DLC coating caused no adverse effects on cells in culture and therefore merits further investigation as a coating for biomedical use. Nowhere in Thomson et al. is there any teaching about corneas or corneal transplants. More specifically, Thomson et al. do not teach or suggest a corneal transplant support consisting of a biopolymer in the shape of a cornea, having a concave and convex side, and having the thickness of an average (or half the average) cornea, and having growth and attachment factors consisting essentially of one or more of the following compounds: laminin, fibronectin, RGDS (SEQ ID NO: 1), bFGF conjugated with polycarbophil, and EGF conjugated with polycarbophil, incorporated *within* the biopolymer, that is suitable for transplantation into a damaged cornea;

The court in *KSR International Co. v. Teleflex Inc.*, 550 US 398, 408, 82 USPQ2d 1385, 1395 (2007) noted that obviousness cannot be proven merely by showing the elements of a claimed device were known in the art; it must be shown that those of ordinary skill in the art would have had some "apparent reason" to combine the known elements in the fashion claimed. *KSR* at 1741. In the same way, when the prior art teaches away from the claimed invention, as shown in Appellant's arguments and other objective evidence, obviousness cannot be proven by merely showing that the biopolymer composition, growth factors or DLC were known, and corneal endothelial cells could be modified by routine experimentation. See, *Ex parte Whalen* II, Appeal 2007-4423, (BPAI July 23, 2008) at pp. 13-16.

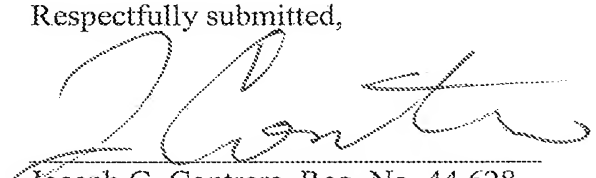
One of ordinary skill in the art, in an attempt to improve corneal endothelial grafts, when reading Parenteau et al., in view of Griffith et al. and Jacob et al., and further in view of Thomson et al., would not have expected that Applicant's invention

would work, because Parenteau et al., Griffith et al. and Thomson et al. do not teach anything about implantable corneal constructs. Further, Griffith et al. teach that only transformed endothelial cells are able to maintain sustained growth in culture. Jacob et al. teaches away from Applicant's claimed invention, because it teaches that RGD is not suitable as an attachment reagent on hydrogels for corneal epithelial cells. Moreover, Thomson et al. suggest that DLC is suitable for orthopedic uses such as joints or bones, which are tissues that are completely different, both structurally and chemically. Therefore, Applicant submits that the combination of Parenteau et al., in view of Griffith et al. and Jacob et al., and further in view of Thomson et al., does not render Applicant's claims 11-12, 14, 17, and 27-28 *prima facie* obvious, because the combination of references do not teach or suggest an acellular corneal transplant support consisting of a biopolymer in the shape of a cornea, having a concave and convex side, and having the thickness of an average (or half the average) cornea, and having growth and attachment factors consisting essentially of one or more of the following compounds: laminin, fibronectin, RGDS (SEQ ID NO: 1), bFGF conjugated with polycarbophil, and EGF conjugated with polycarbophil, incorporated *within* the biopolymer, that is suitable for transplantation into a damaged cornea. Applicant respectfully requests withdrawal of this rejection.

Conclusion

Applicant respectfully submits that the patent application is in condition for allowance. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,



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